PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol to assess the effectiveness and safety of a flexible family visitation model for delirium prevention in adult intensive care units: a cluster-randomized, crossover trial (ICU VISITS STUDY)
AUTHORS	Rosa, Regis; Falavigna, Maicon; Robinson, Caroline; da Silva, Daiana; Kochhann, Renata; de Moura, Rafaela; Santos, Mariana; Sganzerla, Daniel; Giordani, Natalia Elis; Eugênio, Cláudia; Ribeiro, Tarissa; Biasi, Alexandre; Bozza, Fernando; Azevedo, Luciano Cesar; Machado, Flávia; Salluh, Jorge; Pellegrini, José Augusto; Moraes, Rafael; Hochegger, Taís; Amaral, Alexandre; Teles, José Mario; da Luz, Lucas; Barbosa, Mirceli; Birriel, Daniella; Ferraz, Iris; Nobre, Vandack; Valentim, Helen; Corrêa e Castro, Livia; Duarte, Péricles; Tregnago, Rogério; Barilli, Sofia Louise; Brandão, Nilton; Giannini, Alberto; Teixeira, Cassiano

VERSION 1 – REVIEW

REVIEWER	Cheryl Holly Rutgers University USA
REVIEW RETURNED	21-Dec-2017

GENERAL COMMENTS	Dear Authors: this is a very important study as the engagement and role of family in the prevention of delirium is unknown. As this is a study of delirium prevention, it should be more clearly noted: 4. Line 1…Title does not reflect that this is a study of delirium prevention 9. Line 149…this is a study of delirium prevention. What results are anticipated?

REVIEWER	Biren Kamdar University of California, Los Angeles USA
REVIEW RETURNED	18-Jan-2018

GENERAL COMMENTS	In this "ICU Visits" Study, the investigators describe an important and relevant cluster-randomized crossover trial comparing a flexible family visitation model (up to 12 hours) with a restrictive family visitation model (maximum of 4.5 hours). The primary outcome is cumulative incidence of delirium, as measured by trained professionals using the CAM-ICU. Relevant secondary outcomes include delirium-free and ventilator-free days, ICU-acquired infections, length of stay, mortality, family satisfaction, and ICU staff burnout. Overall, the protocol is well written and clear. The 1,650 patient

	study size is ambitious, with 50 patients enrolled in a minimum of 33 different ICUs across Brazil. My major comment/revision involves the statistical handling of delirium as an outcome measure. As the authors know, delirium is a tricky outcome to analyse and interpret, as it fluctuates over time and can often persist after ICU discharge. Therefore, the severity or duration of delirium that patients actually experience is often unknown. Because of this complexity, a "joint modelling" statistical approach is now recommended to account for "competing risks" of coma, death, etc. These issues are well described in the paper "Statistical methods for evaluating delirium in the ICU" by Colantuoni et al. (Lancet Respiratory 2016 Jul;4(7):534-6; PMID 27264776). As delirium comprises the main outcome in this study, I would suggest that the investigators revisit their delirium outcome with a statistician and consider revising the protocol document (methods, limitations, etc), as necessary, to include the Colantuoni (or equivalent) reference and address the complexity of the delirium outcome. Additionally, the CAM-ICU is a subjective instrument, and can be insensitive (van Eijk et al PMID 21562131) when performed by less experienced staff. I would suggest the investigators mention this limitation in their discussion. Finally, I would be curious to know what constitutes "Family Visitation" – if not too late, will the investigators document details of the family visit i.e., who is actually visiting (spouse/child/sibling versus distant relative/friend), what activities they perform (sitting quietly versus talking to the patient), and what language they speak? It would be fascinating to know if different visitations lead to different outcomes.

VERSION 1 – AUTHOR RESPONSE

Editorial Requests:

- Please revise the 'Strengths and limitations' section on page 7 so that it includes one or two limitations.
Authors: We included one study limitation – see line 149, page 7.

- Please include the specific names of the ethics committees that approved this study along with the reference numbers if applicable (this can be provided as a supplementary file if necessary).
Authors: We included the specific names of the ethics committees that approved this study along with the approval numbers – see Supplementary File 3.

Reviewer 1:

Dear Authors: this is a very important study as the engagement and role of family in the prevention of delirium is unknown. As this is a study of delirium prevention, it should be more clearly noted:
4. Line 1…Title does not reflect that this is a study of delirium prevention
Authors: Dr Holly, Thank you very much for your constructive remarks. We modified the title in order to emphasize the main objective of the present study: delirium prevention – See line 1, page 1.

9. Line 149…this is a study of delirium prevention. What results are anticipated?
Authors: We include the term delirium prevention – see line 153, page 7. Our conceptual hypothesis is highlighted in the introduction – see line 2015, page 11.

Reviewer 2:

In this "ICU Visits" Study, the investigators describe an important and relevant cluster-randomized crossover trial comparing a flexible family visitation model (up to 12 hours) with a restrictive family visitation model (maximum of 4.5 hours). The primary outcome is cumulative incidence of delirium, as measured by trained professionals using the CAM-ICU. Relevant secondary outcomes include delirium-free and ventilator-free days, ICU-acquired infections, length of stay, mortality, family satisfaction, and ICU staff burnout.
Overall, the protocol is well written and clear. The 1,650 patient study size is ambitious, with 50 patients enrolled in a minimum of 33 different ICUs across Brazil. My major comment/revision involves the statistical handling of delirium as an outcome measure. As the authors know, delirium is a tricky outcome to analyse and interpret, as it fluctuates over time and can often persist after ICU discharge. Therefore, the severity or duration of delirium that patients actually experience is often unknown. Because of this complexity, a "joint modelling" statistical approach is now recommended to account for "competing risks" of coma, death, etc. These issues are well described in the paper "Statistical methods for evaluating delirium in the ICU" by Colantuoni et al. (Lancet Respiratory 2016 Jul;4(7):534-6; PMID 27264776). As delirium comprises the main outcome in this study, I would suggest that the investigators revisit their delirium outcome with a statistician and consider revising the protocol document (methods, limitations, etc), as necessary, to include the Colantuoni (or equivalent) reference and address the complexity of the delirium outcome.
Authors: Dr. Kamdar, Thank you very much for your constructive remarks. We agree with your elegant inputs regarding the statistical analysis of the burden of delirium. Therefore, we replaced delirium-free days with daily hazard of delirium as secondary outcome (joint modeling approach) – see lines 385, page 19. We also added another tertiary outcome: coma-free days in order to better explore the effects of family presence on patient sedation – see line 402, page 20. We keep the cumulative incidence of delirium as the primary outcome, given that many robust delirium-prevention studies use this outcome (e.g.: Simons KS et al. Lancet Respir Med 2016 [PMID: 26895652]; Su, et al. Lancet 2016 [PMID: 27542303]). We included the reference of Colantuoni in order to justify the choice of daily hazard of delirium as secondary outcome – see 393, page 19 and reference 42.

Additionally, the CAM-ICU is a subjective instrument, and can be insensitive (van Eijk et al PMID 21562131) when performed by less experienced staff. I would suggest the investigators mention this limitation in their discussion.
Authors: We included this limitation and the suggested reference – see line 528, page 25 and reference 48.

Finally, I would be curious to know what constitutes "Family Visitation" – if not too late, will the investigators document details of the family visit i.e., who is actually visiting (spouse/child/sibling versus distant relative/friend), what activities they perform (sitting quietly versus talking to the patient), and what language they speak? It would be fascinating to know if different visitations lead to different outcomes.
Authors: In the present study, we will be able to know the characteristics of family visitors and their attitude during visiting hours. We included one statement in line 404 (page 20) to emphasize that we will evaluate family perception of involvement in patient care as a tertiary outcome, and another statement in line 469 (page 33) to emphasize the fact that we will evaluate family members characteristics.

FORMATTING AMENDMENTS

- Please re-upload your supplementary files in PDF format.

Authors: ok.

OTHER MODIFICATIONS

Authors: We corrected the Ethics approval number of the coordinating site – see line 555, page 26. We also updated the prevision of study finalization – see line 545, page 28, and the number of ICUs that written required informed from patients or proxies – see line 556, page 26. Some minor modifications were performed throughout the manuscript to include the new outcomes: daily hazard of delirium and coma-free days – see abstract and outcomes.

VERSION 2 – REVIEW

REVIEWER	Biren Kamdar University of California, Los Angeles (UCLA) USA
REVIEW RETURNED	03-Mar-2018

GENERAL COMMENTS	The authors have addressed all of my comments satisfactorily; I have no more comments.